Commentary

Repurposing multiple sclerosis drug dimethyl fumarate, a promising fast track candidate for systemic cutaneous T cell lymphoma treatment

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In their recent publication in *Blood*, Nicolay *et al.* (1) report that the immune-modulatory drug dimethyl fumarate (DMF), which is approved for treatment of relapsing-remitting multiple sclerosis (MS) exerts profound effects on cutaneous T cell lymphoma (CTCL) cells from human patients *in vitro* and inhibits tumor growth and distant metastasis in two different animal models of CTCL. Mechanistically, DMF restored the sensitivity of CTCL cells towards apoptosis by down-modulating elevated NF-κB activity in these cells as well as NF-κB-dependent target gene expression in tumor cells. Importantly, this restoration of apoptosis sensitivity was observed only in tumor cells but not in healthy lymphocytes, hence pointing towards a highly attractive tumor-specific mechanism with minor side effects and a well-known safety profile.

CTCL is a non-Hodgkin lymphoma and describes a heterogeneous group of rare lymphoproliferative disorders that exhibit monoclonal proliferation of malignant T lymphocytes primarily homing to the skin (2). From typical patches and plaques in the skin, lymphoma cells may spread and in advanced disease disseminate affecting other organs.

The alterations involved in the induction of malignant T cell transformation are yet to be fully elucidated but very recently mutations in genes involved in T cell activation and apoptosis, NF-κB signaling, chromatin remodeling, and DNA damage response were identified in CTCL cells (3). Functionally it is commonly understood that in CTCL a cell death resistance is the driving phenotype, rather than hyperproliferation, rendering therapy complicated as most cancer treatments aim at the induction of apoptosis. Again multiple factors are involved in the resistance of CTCL cells towards induction of apoptosis; amongst these a constitutive activation of the transcription factor NF-κB has been described (4). Besides anti-apoptotic gene expression NF-κB also regulates immunosuppressive genes in CTCL cells, additionally inhibiting immune responses and contributing to the immunosuppressive nature of the malignant cells (5).

Due to the rarity and heterogeneity of CTCLs, therapy is challenging and although a variety of therapeutic options is available at present, there is no curative approach (6). Moreover, high relapse rates as well as severe side effects and toxicities of the drug regimens used for CTCL treatment are common complications, implying the urgent need for novel therapeutic approaches with higher efficacy rates, milder toxicity profiles and curative potential. Interestingly there is an overlap of drugs implied in CTCL treatment and treatment of autoimmune diseases, including corticosteroids, psoralen ultraviolet A (PUVA), UVB, retinoids, methotrexate and alemtuzumab.

DMF was initially identified as an effective hypoxic cell radiosensitizer (7), in the early nineties licensed in Europe for oral treatment of psoriasis (8) and recently for the treatment of relapsing-remitting MS (9). Besides its well-known induction of the anti-oxidative NRf2 pathway in immune cells (10,11), DMF is a potent inhibitor of NF-κB signaling, which is known to be strongly induced in CTCL cells (4), while showing a limited effect on resting cells (12). The authors hence assumed that in the context of CTCL

a NF-κB targeted therapy would be rather specifically targeting tumor cells but leave bystander T cells unaffected. Of great importance is also the well-known favorable safety profile of the drug with mild side effects, rendering it a highly attractive therapeutic option in comparison to available systemic CTCL drugs with toxicity or adverse effects such as IFN-alpha, bexarotene and methotrexate (6).

Based on these considerations Nicolay *et al.* investigated the effects of DMF with regard to its NF-κB inhibitory properties in CTCL cells in order to clarify whether correction of NF-κB pathway alterations, sensitivity towards apoptosis might be restored in this malignant T cell population. The authors here relied on both *in vitro* experiments with primary CTCL patient cells or CTCL cell lines, as well as in vivo experiments with two distinct animal models.

The *in vitro* experiments revealed that DMF induces apoptosis in patient-derived blood CD4 T cells and in CTCL cell lines, while concomitantly showing only minor effects on healthy donor cells or control cell lines not exhibiting constitutive NF-κB activity. As expected the observed induction of apoptosis was related to the inhibition of NF-κB activity and hence regulation of NF-κB dependent gene transcription. Among the down-regulated genes, the proto-oncogene *bcl-3* gene was most strongly down-regulated. Importantly, bcl-3 is crucially involved in promotion of survival in CTCL as well as involved in induction of NF-κB activity (13). Therefore, DMF-induced Bcl-3 downregulation further perpetuates NF-κB inhibition and hence potentiates the DMF-induced cell death in CTCL cells.

Importantly, the authors were able to corroborate the potential relevance of DMF for control of CTCL cells *in vivo* employing two distinct subcutaneous and intradermal CTCL xenograft mouse models. DMF treatment inhibited CTCL tumor growth, tumor spreading to distant organs and improved survival. Of interest, while DMF enhanced cell death both in primary tumors as well as in metastases, it only marginally affects the surrounding tissues. Also none of the DMF treated mice showed acute side effects, indicating high tolerability of the drug.

With their data the authors establish DMF as a promising novel therapeutic option in CTCL, demonstrating a direct effect on NF-κB in these cancer cells, which is in contrast to prior studies addressing drugs that exert their effects on NF-κB only indirectly by targeting other signaling pathways (14,15).

In both, the development of cancer and autoimmunity a failure of the immune system is given. In CTCL the malignant cells elicit suppression of cell-mediated immunity and exhibit decreased production of pro-inflammatory cytokines. Moreover, these cells are very versatile and can share features with either immune-suppressive regulatory T cells or proinflammatory IL-17A-producing helper T cells depending on the stimuli received. Mechanistically, IL-2-type cytokines activate STAT5 to promote expression of Treg-related FoxP3, while various cytokines can activate STAT3 to induce synthesis of IL-10 and IL-17 (16). In the early stages of CTCL immune evasion occurs under a regulatory cell phenotype, allowing the clonal T cells to expand. During later stages the cells lose FoxP3 expression but continue to express an immunosuppressive cell-surface ligand PD-L1 (16).

On the other hand, in T cell-mediated autoimmunity, effector T cells escape regulatory mechanisms causing an immune disbalance that needs to be controlled by immune therapeutic approaches that dampen overshooting effector T cell responses (17). In contrast to monoclonal antibodies depleting cell populations such as alemtuzumab and ocrelizumab, or very specific approaches e.g., blockade of the high-affinity IL-2 receptor via daclizumab, DMF exerts pleiotropic effects in immune cells via modulation of distinct intracellular pathways such as HCAR2, nrf2, as well as NF-κB (10,18). Hence, DMF represents an attractive candidate for drug repurposing due to the combination of promising mechanism of action and well-known safety profile and therapeutic experience in psoriasis and MS, respectively. Such drug repurposing has gained much interest recently due to decreased costs for clinical research, faster clinical development and increased success rates (19) and has been suggested for DMF in other indications before (20).

Interestingly, while in T cell-mediated autoimmunity DMF-mediated effects are mediated via the Nrf2 and HCAR2 pathways, in CTCL proapoptotic effects exerted via NF-κB inhibition seem to be pivotal. This suggests that DMF exerts qualitatively different effects on malignant T cells versus autoreactive T cells. Besides the favorable side effect profile of such an immune-modulatory drug this approach is particularly attractive as the strong proapoptotic effect elicited by DMF is restricted to cancer cells with NF-κB over reactivity. Moreover, it seems feasible to combine DMF with other therapeutic strategies such as HDAC inhibitors, bexarotene or interferons (1). Of note, although not approved for MS, some therapeutic concepts applied in CTCL such as UVB radiation and retinoids proved effective in control of T cell-mediated

CNS autoimmunity in animal models (21,22), suggesting that other similarities exist between autoimmune T cell responses and CTCL with regard to therapeutic targets.

Currently the authors are recruiting CTCL-patients for a phase II clinical trial (ClinicalTrials.gov Identifier: NCT02546440) with the objective to investigate whether oral treatment with DMF is leading to a significant improvement after 24 weeks of treatment. Such fast translation of a scientific concept into a clinical trial is notable and reflects the high potential of this approach—both with regard to efficacy and feasibility in the context of CTCL.

Taken together Nicolay *et al.* present a promising data set that, not only further elucidate the role of NF-κB in CTCL, but show promising results for repurposing the MS drug DMF to a malignant disease with so far limited therapeutic options.

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Footnote

Conflicts of Interest: M Herold has no conflicts of interest to declare. L Klotz received compensation for serving on Scientific Advisory Boards for Genzyme and Novartis; she received speaker honoraria and travel support from Novartis, Merck Serono and CSL Behring; she receives research support from Novartis and Biogen Idec.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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